REMARKS

I. Status of the Application

Claims 53-60, 62, 64, and 66-67 are pending. Applicants herein amend Claims 53 and 66 to include the elements "Substance P", "nerve growth factor", and "at a temperature of 0–4°C", and cancel Claims 61 and 63, in order to further their business interests and the prosecution of the present application, yet without acquiescing to the Examiner's arguments. Therefore, Claims 53-60, 62, 64, and 66-67 are presently pending.

Support for the inclusion of the elements "Substance P" and "nerve growth factor" are found throughout the specification including at least in paragraphs [0009]-[0014], paragraph [0017], paragraph [0092], Table 11, Table 12, Table 14, Table 14, Table 15, Table 16, Table 17, and Examples 2-8. Support for the inclusion of the element "at a temperature of 0–4°C" is found at least in paragraphs [0005] and [0150]. Therefore, the amendments are fully supported by the specification. No new matter is introduced.

II. Claim Rejections Under 35 U.S.C. § 103(a)

The Examiner objected to Claims 53, 56, 59-60, 63, and 66 under 35 U.S.C. 103(a) as allegedly unpatentable over Petrinec *et al.* (Surgery (1996) 120, 221-225; hereinafter "Petrinec") in view of Steffen *et al.* (Transplant Int. (1990) 3, 133-136; hereinafter "Steffen") and Tavakkol *et al.* (Arch. Dermatol. Res. (1999) 291, 643-351; hereinafter "Tavakkol").

The Examiner objected to Claims 57-59 under 35 U.S.C. 103(a) as allegedly unpatentable over Petrinic *et al.* in view of Steffen *et al.*, Tavakkol *et al.* as applied to Claim 53, and in further view of Janoff *et al.* (U.S. Pat. No. 5,766,624; hereinafter "Janoff") and Hancock *et al.* (U.S. Pat. No. 6,172,185 B1; hereinafter "Hancock").

The Examiner objected to Claims 61-62 under 35 U.S.C. 103(a) as allegedly unpatentable over Petrinec *et al.* in view of Steffen *et al.*, Tavakkol *et al.* as applied to Claim 53, further in view of Nishida *et al.* (J. Cell. Physiol. (1996) 169, 159-166; hereinafter "Nishida").

The Examiner objected to Claims 63-64 under 35 U.S.C. 103(a) as allegedly unpatentable over Petrinic *et al.* in view of Steffen *et al.*, Tavakkol *et al.* as applied to Claim 53, in further view of Lambiase A. (U.S. Pat. No. 6,537,808 B2; hereinafter "Lambiase").

The Examiner objected to Claim 67 under 35 U.S.C. 103(a) as allegedly unpatentable over Petrinec *et al.* in view of Steffen *et al.*, Tavakkol *et al.*, Nishida *et al.*, and Lambiase.

The Examiner's arguments hinge on the assertion that Tevakkol *et al.* teach that "…the IGF-1 concentration (2-10 ng/ml) taught by Tavakkol *et al.* is particularly useful in the organ culture for human organ preservation…." (Office Action of November 12, 2008, page 4).

Applicants respectfully disagree with this assertion, as detailed *infra*. Applicants further assert that, contrary to the Examiner's assertions, Janoff *et al.*, Hancock *et al.*, and Nashida *et al.* fail to teach or suggest each element of the claims and in fact teach away from the present invention, as detailed *infra*.

III. The Claims Are Not Obvious

In rejecting claims under 35 U.S.C. § 103, the Examiner bears the initial burden of presenting a *prima facie* case of obviousness.[1] A *prima facie* case of obviousness is established when the teachings from the prior art itself would appear to have suggested the claimed subject matter to a person of ordinary skill in the art.[2] An obviousness analysis requires that the prior art both suggest the claimed subject matter and reveal a reasonable expectation of success to one reasonably skilled in the art.[3]

The test for *prima facie* obviousness is consistent with legal principles enunciated in *KSR Int'l Co. v. Teleflex Inc.,* 127 S. Ct. 1727 (2007). The Federal Circuit summarized the Supreme Court's holding in *KSR* that "While the *KSR* Court rejected a rigid application of the teaching, suggestion, or motivation ("TSM") test, the Court acknowledged the importance of identifying 'a ***reason*** that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does' in an obviousness determination." *Takeda Chem. Indus., Ltd. v. Alphapharma Pty., Ltd., 06-1329, slip op. (Fed. Cir. June 28, 2007)*, at 13-14 (quoting *KSR,* 127 S. Ct. at 1731) (emphasis added). Although the TSM test should not be applied in a rigid manner, it can provide helpful insight to an obviousness inquiry. *KSR,* 127 S. Ct. at 1731. The *KSR* Court upheld the secondary considerations of non-obviousness, noting that there is "no necessary inconsistency between the idea underlying the TSM test and the

[1] See In re Rijckaert, 9 F.3d 1531, 1532, 28 USPQ2d 1955, 1956 (Fed. Cir. 1993).
[2] In re Bell, 991 F.2d 781, 783, 26 USPQ2d 1529, 1531 (Fed. Cir. 1993).
[3] In re Vaeck, 947 F.2d 488, 493, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991).

Graham analysis." *Id.* Additionally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. See M.P.E.P. 2143.

A. The Cited References Fail to Teach or Suggest Each Element of the Claims, And Actually Teach Away From The Invention

Applicants respectfully submit that the cited references do not render the amended claims *prima facie* obvious because the cited references do not teach, suggest nor enable each element of the claims.

In the rejection of 53, 56, 59-60, 63, and 66, the Examiner concedes that Petrinec *et al.* do not expressly teach a composition comprising an internal organ, lactobionate, and IGF-1 at a concentration of between 1-100 ng/ml, and attempts to combine the teachings of Petrinec *et al.* with those of Steffen *et al.* and Tavakkol *et al.* to remedy these deficiencies.

Tavakkol *et al.* teach methods specific to culturing of skin punch biopsies at 37°C. Clearly, skin punch biopsies are distinct from "internal organs" as recited in Claim 53. One cannot object to what has not been claimed. As one of ordinary skill in the art immediately appreciates, skin culturing methods are distinct from the methods of the present invention. Specifically, an artisan of ordinary skill realizes – as is clearly taught in Tevakkol *et al.* – that skin has unique requirements for exogenous Ca^{2+} levels in comparison to internal organs, and a lack of adequate Ca^{2+} in media used for skin punch biopsy culturing leads to necrosis. This fact in itself is evidence that methods for culturing skin punch biopsies are distinct from methods appropriate for *ex vivo* storage of internal organs. Furthermore, in contrast to the Examiner's assertions, Tevakkol *et al.* did <u>not</u> find that exogenous IGF-1 at a level of 2-20 ng/ml could prevent necrosis of skin punch biopsies during culturing. To the contrary, Tevakkol *et al.* state with regard to addition of growth factors to low-calcium media:

> "<u>Neither [IGF-1 at 2 ng/ml nor EGF at 10 ng/ml] prevented degeneration of the tissue</u> as reflected in the histological appearance of the growth factor-treated tissue and in the quantitative data….IGF-1 concentrations as high as 20 ng/ml and EGF concentrations as high as 50 ng/ml were used with identical results." (Tavakkol *et al.*, page 646, paragraph 3 through page 647, paragraph 1; emphasis added)

The Tevakkol *et al.* study did not teach preservative or restorative properties of IGF-1 in skin culture methods. Rather, the authors taught that presence of adequate exogenous Ca^{2+} levels are needed to avoid necrosis in their culturing system, and that while endogenous IGF-1 was necessary to mediate the requirement for and effect of Ca^{2+}, exogenous IGF-1 was a wholly inadequate substitution for Ca^{2+}.

Therefore, as one of ordinary skill in the art immediately appreciates,

1) the teachings of Tavakkol *et al.* do not pertain to storage of internal organs, as compositions developed for skin culture are distinct from methods used for *ex vivo* storage of internal organs; and regardless,

2) Tavakkol *et al.* do not in fact teach that IGF-1 at a concentration of 1-100 ng/ml finds use in protection of cultured skin punch biopsies against necrosis.

Therefore, one of ordinary skill in the art would have had no motivation to combine the teachings of Tevakkol *et al.* with the teachings of Petrinec *et al.* and Steffen *et al.*, and even if doing so, would have had no expectation of success.

The examiner relies on the teachings of Petrinec *et al.*, Steffen *et al.*, and Tavakkol *et al.* for all other claim rejections on the basis of 35 U.S.C. § 103(a). Because the cited references do not teach all elements of the claim (and in fact teach away from the methods of the present inventions) as described *supra*, accordingly all other claim rejections are improper. However, Applicants respectfully assert that Janoff *et al.*, Hancock *et al.*, and Nashida *et al.* in fact each teach away from the present invention.

In rejecting Claims 56-59 as allegedly unpatentable over Petrinec *et al.*, Steffen *et al.*, and Tavakkol *et al.*, the Examiner concedes that Petrinec *et al.* "do not expressly teach that the composition further comprises an antimicrobial peptide" (Office Action of November 11, 2008, page 5). The Examiner attempts to remedy this deficiency through combination with the teachings of Janoff *et al.*, asserting that Janoff *et al.* "…teach antimicrobial peptide defensin (claims 56-57), e.g., indolicin (col. 3, lines 23), has ability of not only inhibiting and preventing microbial infection or fungus infection…but also useful for organ transplantation…" (Office Action of November 11, 2008, page 5). Applicants respectfully assert that this statement completely misconstrues the teachings of Janoff *et al.* Firstly, Janoff *et al.* state:

> "Anti-infective effective amounts of the pharmaceutical composition may be administered to animals for the treatment or prevention of infections by organisms

> sensitive to a defensin, e.g., indolicin. Preferred therapeutic subjects are mammals, particularly, humans, for example those humans whose immune systems have been compromised, e.g., by viruses such as HIV, by chemotherapy or for organ transplantation." (Janoff *et al.*, column 3 paragraph 5 through column 4 paragraph 1; emphasis added.)

One of ordinary skill in the art immediately appreciates that a therapeutic method comprising administration of defensin peptide to an immunocompromised subject is completely distinct from an *in vitro* composition comprising an internal organ, lactobionate, and IGF-1 at a concentration of 1-100 ng/ml as recited in Claim 53 of the instant application. It does not matter whether the subjects referred to in Janoff *et al.* experience an immunocompromised state due to the immune-suppressing regimes that are given to organ transplant recipients, or whether the immunocompromised state occurs through any other disease state, condition, or action. Simply put, the methods taught in Janoff *et al.* are immaterial to the present invention, as the instant application does not claim a therapeutic composition to be administered *in vivo*.

Furthermore, Janoff *et al.* actually teach away from the use of defensin peptide as embodied in compositions of the present invention. Janoff *et al.*state:

> "Achieving the full therapeutic potential of defensins in animals requires that the proteins be administered in such a way that they reach their targets in an active form but avoid collateral damage to the animal's normal cells. This may be accomplished by entrapping the defensins in liposomes." (Janoff *et al.*, column 2, paragraph 1)

Therefore, Janoff *et al.* without fail teaches the necessity of liposome-encapsulated defensins for therapeutic use. Furthermore, even where non-liposome-encapsulated indolicidin is used *as a control*, for example in Table 8, Janoff *et al.* show that free indolicin can result in up to 100% hemolytic activity (that is, lysis of red blood cells *in vitro*). As one of ordinary skill in the art immediately appreciates, hemolysis is an undesirable event in *ex vivo* storage of internal organs. Thus, one of ordinary skill in the art would have had no motivation to combine the teachings of Janoff *et al.* with the teachings of Petrinec *et al.*, Steffen *et al.*, and Tevakkol *et al.*, and even if doing so, would have had no expectation of success.

In rejecting Claims 56-59, the Examiner further combines the teachings of Hancock *et al.* to remedy the deficiencies of Petrinec *et al.*, Steffen *et al.*, Tevakkol *et al.*, and Janoff *et al.*

In making this argument, the Examiner states that "Hancock *et al.* teach a defensin peptide "RLSRIVVIRVCR" of SEQ ID NO:3 (see abstract) which has sequence identity to instant SEQ ID NO:38 (claim 58)" (Office Action of November 11, 2008, page 5). This assertion is, quite simply, completely erroneous. The amino acid of Hancock *et al.* SEQ ID NO:3 is not the same as the SEQ ID NO:37 of the instant application. Specifically, SEQ ID NO:37 of the instant application recites RL**C**RIVVIRVCR, not RL**S**RIVVIRVCR as is recited in Hancock *et al.* Applicants respectfully assert that it is improper to reject what has not been claimed.

Finally, in rejecting Claims 61-62 as allegedly unpatentable over Petrinec *et al.*, Steffen *et al.*, and Tavakkol *et al.*, the Examiner concedes that Petrinec *et al.* "do not expressly teach the composition further comprises further comprises [sic] substance P", and attempts to remedy this deficiency by combination with the teachings of Nishida *et al.* However, Applicants assert that Nishida *et al.* do not teach the use of substance P for the preservation of internal organs, for example in *ex vivo* low temperature storage.

In seeking to understand the process of epithelial cell migration in cultured tissue, Nishida *et al.* teach the use of a specialized model system involving cut sections of corneal tissue which is cultured at 37°C, and to which corneal epithelial cells are applied to determine the attachment and migration properties of said corneal epithelial cells. One of ordinary skill in the art immediately appreciates that this specialized system is completely unrelated to the composition of the present invention, and that methods and compositions used in corneal epithelial cell attachment and migration assays have no bearing on *ex vivo* storage of internal organs. Any effect of Substance P on the assay of Nishida *et al.* is irrelevant to the composition of the present invention, because the biological processes of *ex vivo* internal organ storage and corneal epidermal cell attachment and migration are entirely different. Thus, one of ordinary skill in the art would have had no motivation to combine the teachings of Nishida *et al.* with the teachings of Petrinec *et al.*, Steffen *et al.*, and Tevakkol *et al.*, and even if doing so, would have had no expectation of success.

Accordingly, Applicants respectfully submit that because the cited references, individually or in combination, do not teach, disclose or suggest each limitation of the claims, the cited references do not render the presently claimed invention *prima facie* obvious.

Furthermore, Applicants submit that because Claims 53 is not obvious, then Claims 54-64 also cannot be obvious because they all depend from a nonobvious claim. (See, e.g., In re

Fritch, 972 F.2d 1260, 1266 (Fed. Cir. 1992) ("[D]ependent claims are nonobvious if the independent claims from which they depend are nonobvious."))

B. The Claims Are Novel Over Teachings Of The References, Whether References Are Considered Singly Or In Combination

Applicants respectfully submit that the cited references, individually or in combination, do not teach, suggest nor enable each element of the claimed invention, thereby precluding a finding of *prima facie* obviousness. Additionally, the cited references fail to provide a reasonable expectation of success for carrying out the claimed invention.

As described *supra*, the references whether considered singly or in combination do not teach all elements of the claimed invention, i.e. an *in vitro* composition comprising an internal organ, lactobionate, and recombinant insulin-like growth factor 1, wherein recombinant Insulin-like Growth Factor 1 is provided at a concentration of from about 1 ng/ml to 100 ng/ml, for example as per Claim 53; or wherein the composition further comprises a defensin peptide for example as per Claims 57 and 58; or wherein the composition further comprises Substance P for example as per Claim 61. For example, Tevakkol *et al.* do not teach the use of IGF-1 in the range of 1-100 ng/ml as an internal organ-preserving agent in *ex vivo* storage. Furthermore, Janoff *et al.* do not teach the use of a defensin peptide as an internal organ-preserving agent in *ex vivo* storage; neither does Hancock *et al.* teach SEQ ID NO: 37 of the instant application. In addition, Nishida *et al.* do not teach the use of Substance P as an organ-preserving agent in *ex vivo* storage. Therefore the elements claimed in the instant application are novel over the teachings of the cited references.

C. The Cited References Fail to Enable the Claimed Invention

The cited references, individually or in combination, not only fail to teach or suggest the claims, they also fail to enable the claimed systems and methods of using the same of the present invention. To the extent that the Examiner alleges as much, Applicants respectfully submit that none of the examples or experimental data in any of the references provide any details regarding the use of IGF-1 in the range of 1-100 ng/ml in an *in vitro* composition comprising an internal organ, lactobionate, and IGF-1. Similarly, none of the examples or experimental data in any of the references cited provide any details regarding the use of a defensin peptide in said

composition, nor for the use of SEQ ID NO: 37, nor for the use of Substance P. The lack of such detail has been found by the Federal Circuit to be an important consideration in an obviousness analysis:

> "Moreover, it stands to reason that if the disclosure of a useful conjugate protein and the method for its cleavage were so clearly within the skill of the art, it would have been expressly disclosed in the specification, and in the usual detail. Patent draftsmen are not loath to provide actual or constructive examples, with details, concerning how to make what they wish to claim."[4]

Indeed, the lack of any reference, detail or explanation concerning the claimed methods of the present invention raises an enablement issue. Applicants respectfully submit that to render a claim obvious a cited reference must enable one of ordinary skill in the art to make and use the invention.[5]

> "[W]hen there is no disclosure of any specific starting material or of any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art. It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement."[6]

Quite simply, the cited references fail to provide, or even to suggest, a single working example of a method or system of the presently claimed invention.

Thus, none of the cited references, individually or in combination, render the claimed invention *prima facie* obvious. Applicants respectfully request that rejections under 35 U.S.C. § 103 be withdrawn and that the claims be passed to allowance.

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[4] See *Genentech, Inc., v. Novo Nordisk*, 108 F.3d 1361 (Fed. Cir. 1997).
[5] See *Beckman Instruments v. LKB Producter AB*, 892 F.2d 1547, 1551; 13 USPQ2d 1301, 1304 (Fed. Cir. 1989).
[6] See *Genentech, Inc., v. Novo Nordisk*, 108 F.3d 1361 (Fed. Cir. 1997)

CONCLUSION

For the reasons set forth above, it is respectfully submitted that Applicants have addressed all grounds for rejection and Applicants' claims should be passed to allowance. Reconsideration of the application is respectfully requested. Should the Examiner believe that a telephone interview would aid in the prosecution of this application, Applicants encourages the Examiner to call the undersigned collect at (608) 218-6900.

Respectfully submitted,

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